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Breast-Conserving Surgery or Mastectomy?

Impact on Survival

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Introduction: The early randomized controlled trials revealed no differences in survival between breast-conserving surgery (BCS) and mastectomy. However, breast cancer treatment has undergone changes, and the results of recent population-based registry studies suggest superior long-term survival after BCS. To explore the current evidence, a systematic review and meta-analysis of population-based observational studies from 2010 and onward was conducted.

Methods: A literature search was conducted in the PubMed, Embase, and Cochrane databases to identify relevant literature. Keywords included "mastectomy," "breast conserving surgery," and "survival." The identified studies were narratively reviewed and effect sizes (hazard ratios [HRs]) for overall (OS) and breast cancer-specific survival (BCSS) were combined with random-effects models.

Results: A total of 30 reports were included in the review, and results from 25 studies were included in the meta-analyses. Compared with mastectomy, BCS was associated with better OS (HR = 1.34 [1.20–1.51]; N = 1,311,600) and BCSS (HR = 1.38 [1.29–1.47]; N = 494,267). Selected subgroups of patients, based on lymph node status, age (<50 years/≥50 years), and radiation therapy after mastectomy (±), all showed better overall survival after BCS. The number (range 4–12) and type of prognostic variables adjusted for in the survival analyses of the studies did not statistically significantly moderate the differences in survival between BCS and mastectomy.

Conclusions: The combined findings from large population-based studies indicate that BCS is associated with survival benefit compared with mastectomy, suggesting that BCS be the recommended treatment of early breast cancer (T1-2N0-1M0) if a radical lumpectomy can be performed.

Keywords: breast conserving surgery, mastectomy, survival, breast cancer specific survival, breast conserving surgery vs. mastectomy, BCS

Breast-conserving surgery (BCS) was introduced in the 1980s after randomized controlled trials (RCTs) had documented adequate local control and equivalent survival.[1] Long-term follow-up studies confirmed the initial results.[2–5] Although the long-term follow-up studies were published relatively recently in 2002,[2,3] 2008,[4] and 2016,[5] the comparable survival of BCS and mastectomy has generally been observed for patients treated several decades ago. Breast cancer treatments have since improved, and in the recent decades, BCS combined with radiation therapy (RT) to the residual breast has become the gold standard in the treatment of early breast cancer, used in approximately 7 of 10 patients.[6]

Although there are no new RCTs comparing BCS with mastectomy, several single, multicenter, and population-based registry studies have evaluated the outcome of the type of surgery in recent years.[7–10] Even though the level of evidence from such studies is lower than from RCTs, the results provide important information about the treatment of unselected patients. Some population-based observational studies confirm that the outcome after BCS is at least as favorable as after mastectomy,[11,12] but most studies suggest that long-term survival after BCS may even be superior to survival after mastectomy.[7,13,14] Furthermore, it is unclear whether treatment-associated differences in survival may be moderated by differences between patients in demographic and disease characteristics, for example, age, lymph node involvement, and whether mastectomy is combined with RT or not. It could also be of interest to compare possible differences in survival across regions, as treatment standards may vary between, for example, North America and Europe. Increased knowledge about possible differences between BCS and mastectomy in both overall and breast cancer-specific survival and possible moderators of such differences is of urgent interest to clinicians.

To the best of our knowledge, no systematic review and meta-analysis has included the recently published, population-based studies. Our aim was, therefore, to fill this gap in our knowledge by conducting a systematic review and meta-analysis of the available population-based observational studies published from 2010 and onward.

METHODS

This systematic review and meta-analysis was preregistered with PROSPERO (reg. no. CRD42021272711) and is reported

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in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[15]

Search Strategy and Selection Criteria

A systematic keyword-based search was conducted by the investigators in the Embase, PubMed, and Cochrane databases for the period from January 1, 2010, to June 30, 2021 (final search July 3, 2021) using a combination of MESH-terms and keywords referring to "mastectomy," "breast conserving surgery," and "survival." No further restrictions were applied. The search was supplemented by hand-searching for potentially relevant articles in the reference lists of retrieved articles. Based on the population, intervention, comparator, outcome (PICO) approach,[16] the studies were eligible for inclusion if (1) the population studied included patients with breast cancer, (2) a proportion of the sample had been treated with BCS, (3) were compared with patients treated with mastectomy, and (4) provided data on overall survival (OS) and breast cancer-specific survival (BCSS). Studies had to be population-based observational studies, and we excluded RCTs and hospital-level single- or multicenter studies. Only English-language reports in peer-reviewed journals were considered, and we excluded the "grey literature," for example, conference abstracts and dissertations. Study selection was performed independently by 2 authors (PC, AB). Data extraction was performed independently by pairs of authors from a group of 3 (PC, AB, MM). Disagreements were resolved through negotiation. When studies presented results for the same or overlapping samples, the study with the largest number of patients was included in the meta-analyses.

Data Extraction

The data extracted were hazard ratios (HR) and their 95% confidence intervals for (a) OS and (b) BCSS of BCS *versus* mastectomy. If the original publications reported the results as mastectomy versus BCT, the reciprocal values were calculated (1/original value) and used in the meta-analyses. Additional data extracted were (c) the number of patients in each analysis, (d) the prognostic covariates adjusted for in the survival analysis, for example, tumor characteristics (T-stage, N-stage, localization, type, grade, hormone- and HER2-receptor status, lymphovascular invasion), patient characteristics (age, comorbidity), and treatments (RT, chemotherapy [CT], endocrine therapy [ET], anti-HER2 treatment), (e) whether patients treated with mastectomy had received RT or not, (f) any special restrictions of the sample (e.g., nodal status [N0, N+], age group, triple negative breast cancer [TNBC]), (g) follow-up time (months), and (h) region (North America, Europe, Asia, Oceania).

We tried to obtain additional information from a single study about the number of patients who had received radiation treatment.[17] Unfortunately, the researchers were not able to supply the requested information.

Study Quality and Certainty of Evidence

The Newcastle-Ottawa Quality Assessment Scale (NOQAS) for cohort studies[18] was used to evaluate the risk of bias in the included studies. The studies were rated independently by 2 authors (NR, MM), and disagreements resolved through negotiation. The robvis tool[19] was used to provide a visual summary of the risk of bias. The certainty of available evidence was assessed with the GRADE method.[20]

Meta-analytical Strategy

Observational cohort studies were subjected to random effects meta-analysis to ascertain the pooled overall effect estimate and its precision. To aid the interpretation of the results, we conducted, as a supplement to the conventional frequentist meta-analysis, a Bayesian Model-Averaged meta-analysis.[21]

Pooling Effect Sizes

An inverse variance-weighted random-effects model considering the precision of each study was used in all analyses, with hazard ratios larger than 1.0 taken to indicate an effect in the direction of BCS associated with increased OS and BCSS. For studies reporting relevant data, results of comparisons in separate subgroups, for example, between BCS and mastectomy plus RT or BCS and mastectomy minus RT (Mx+RT and/or Mx-RT), in lymph node negative (N0) and lymph node positive (N+) patients, in younger (age <50 years) and older patients (age ≥50 years), and in North American and European studies, were analyzed separately. The individual and pooled hazard ratios are presented in forest plots. Sensitivity analyses were planned for the evaluation of the influence of possible outliers (defined as ± 2 standard deviations from the pooled estimate).

Heterogeneity

Heterogeneity was investigated using Q and I^2 statistics.[22] Heterogeneity tests aim at determining to which degree the variation in effect sizes reflects true differences (heterogeneity) or sampling error. The I^2 value is an estimate of the between-study variance in a pooled effect estimate that is accounted for by heterogeneity of the effect sizes in the included studies and is assumed to be relatively unaffected by the number of studies.[23] If the results indicated heterogeneity ($I^2 > 0.0$), we calculated the 95% prediction interval, which estimates the expected range of true effects in 95% of future studies.[24]

Publication Bias

The possibility of publication bias was assessed using funnel plots and Egger's test for pooled results of 10 or more effect sizes.[25] If results were suggestive of possible publication bias, we planned to conduct sensitivity analyses by imputing the "missing studies" and calculating adjusted effect estimates using the Duval and Tweedie trim-and-fill method.[26]

Moderator Analyses

To explore possible sources of heterogeneity ($I^2 > 0.0$), we used meta-regression (random-effects, maximum likelihood method) to examine the associations between the effect size and a number of possible categorical and continuous moderators, including (a) lymph node positive status (referent: lymph node negative), (b) older age (≥ 50) (referent: age < 50), (c) number of demographic, tumor-, and treatment-related factors adjusted for in the survival analysis, (d) studies conducted in North America (referent: Europe), (e) median follow-up time in months, and (f) high risk of bias (referent: low risk of bias). The frequentist analyses were performed using Comprehensive Meta-Analysis, version 3.[27]

Supplementary Bayesian Analysis

A supplementary Bayesian Model-Averaged meta-analysis[21] of the associations between surgery type and survival examined the results of 4 models: (a) fixed-effect null hypothesis (fH0), (b) fixed-effect alternative hypothesis (fH1), (c) random-effects null hypothesis (rH0), and (d) random-effects alternative hypothesis (rH1). Bayesian Model-Averaged analysis thus avoids selecting either a fixed- or random-effects model and addresses 2 questions in light of the observed data: What is the plausibility that the overall effect is nonzero and is there between-study variability in the effect size? We chose an uninformed prior probability,

that is, 25%, of each of the 4 models and 2,000 iterations. Concerning parameter distributions, we chose previously recommended defaults.[21] We thus used a zero-centered Cauchy prior with a scale of 0.707 for the effect size. To have zero indicating the null effect, the hazard ratios and the upper and lower limits were log-transformed. For the between-study variation, we used an empirically informed prior distribution of nonzero between-study deviation estimates based on effect sizes from 705 meta-analyses published in Psychological Bulletin between 1990 and 2013.[28] This distribution has been approximated by an Inverse-Gamma (1, 0.15) prior on the standard deviation (Tau).[21] The supplementary Bayesian analyses were conducted with JASP, version 0.14.1.[29]

RESULTS

Study Characteristics

A total of 878 studies were found after removal of duplicates and screened for eligibility by title and abstract leaving 75 for full-text assessment. A total of 30 study reports were included in the review (Fig. 1), with 20 from North America, 7 from Europe, 2 from Asia, and 1 from Oceania. The studies reported survival data for patients treated between 1990 and 2014 (Table 1). One study[9] reported on 2 separate populations. The population sizes ranged from 1,784 to 845,136 patients with a total of 2,343,878 (BCS, mastectomy) patients in the included studies. There is considerable overlap with several studies based on cohorts from the same registries. Thus, there were several publications from the US based on the database from the Surveillance, Epidemiology, and End Results (SEER) Program[30–38] and the National Cancer Database (NCDB),[6–21] and there were also several studies based on the national registries in Norway[8,39,40] and the Netherlands.[9,13,41]

The tumor characteristics varied considerable between studies. All included information on tumor size and nodal status, but information on hormone receptor status was lacking in 7 reports[7–9,11,33,36,42] and HER2-status was only available for 10 studies.[9,10,14,35,38,39,44–46,50] Data on systemic treatment were sparse and completely lacking in 10 studies,[7,8,30,31,35–38,40,50] and HER2-directed treatment was only reported in a single study.[14]

Follow-up times ranged from 22 to 144 months and was not reported in 9 studies (Table 1). Five-year OS was reported in 15 studies. Most studies reported a better 5-year OS after BCS compared with mastectomy (range 2–22%). One study[11] reported on a cohort restricted to tumors larger than 5 cm, where the OS was similar in the two groups (1% improved survival after mastectomy). Likewise, the 10-year OS was better after BCS (range 4–25%) in the 10 studies reporting on this outcome.

Three SEER-studies focused on triple negative breast cancer (TNBC) alone. Chen, Wang et al[33] looked at a population treated 2010–13, and Li et al[35] reported on a material from 2010 to 2014. These 2 materials have some overlap, but Li et al restricted the material to node negative patients (N = 14,910), whereas Chen, Wang et al also included N1–4 patients (N = 11,514). Very recently, Guo et al published on a SEER population from 2010 to 2015 (N = 13,262) overlapping both the previous studies. All 3 studies showed a better outcome after BCS with reported differences in OS: 9% (4 years), 5% (5 years), and 8% (5 years), respectively (Table 1). One further study reported on metaplastic breast cancer (N = 2,412) and described a remarkable 22% better 5-year OS after BCS.[47]

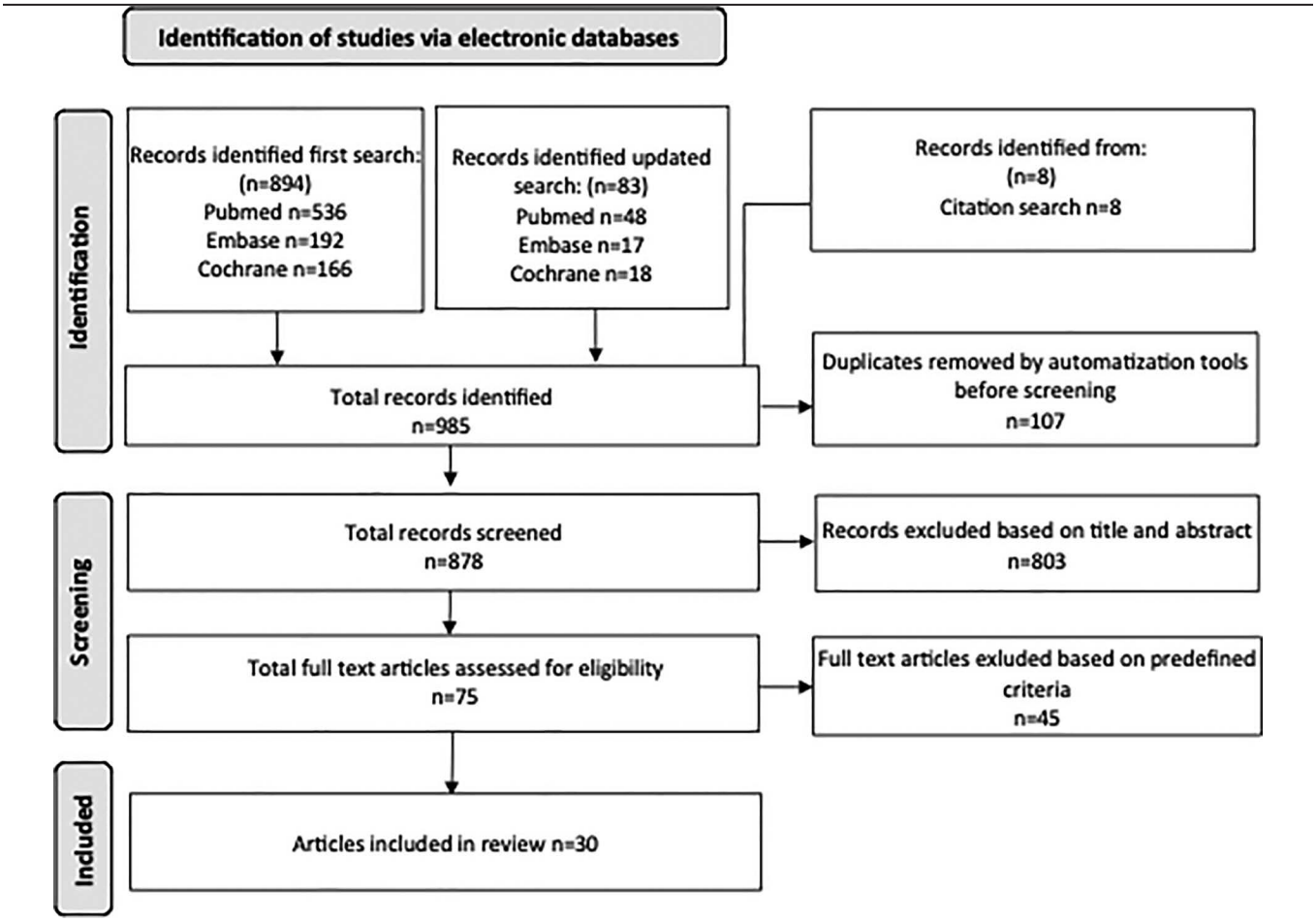


FIGURE 1. Flowchart describing the literature search through the databases of PubMed, Embase, and Cochrane.

TABLE 1.

Description of the 30 Population-based Studies Included in the Review

Author, year	Population, Country	Number of Patients	Included Patients	Tumor Characteristics	Treatment Data	Comorbidity	Follow-up Months	Survival Data	Stratified Analysis
Mahmood et al 2012[30]	SEER, USA 1990–2009	14,764: B 6640, M 8124	T1-2N0-1M0 Age 20–39	TS (10 mm groups), LN, type, grade, ER, PgR	RT	No	68 mo	5-yr OS: B 92.5% M 83.5%	Age
Hwang et al 2013[7]	California, USA 1990–2004	112,514: B 61,771, M 50,383	T1-2N0-1M0	TS, LN, grade	RT	No	110 mo	10-yr OS: age <50/HR– B 81%, M 75% Age ≥50/HR+ B 92%, M 87%	<50HR–, <50HR+, ≥50HR–, ≤50HR+
Jeon et al 2013[42]	South Korea 1988–2006	3512 B 1951 M 1561	T1N0-1M0 Age ≤40	T-stage (T1a, T1b, T1c), N-stage (N0, N1)	CT ET	No	111	10-yr BCSS B 96.9%, M 94.9%	N-stage (N0, N1)
Agarwal et al 2014[31]	SEER, USA 1998–2009	132,149: B 92,671, M 34,999 (4479)	T≤40 mm, N0-1M0	TS (0-2, 2-4), LN ER, PgR, grade	No	No	?	5-yr BCSS: B 97%, M 94%, M+RT 90% 10-yr BCSS: B 95%, M 90%, M+RT 83%	Mx-RT, Mx+RT
Hartmann-Johnsen et al 2015[8]	Norway 2002–2010	13,015: B 8065, M 4950	T1-2N0-1M0	TNM-stage, type, grade	No	No	87–104 mo	5-yr OS: B 95% M 80%	Age < 50
Fisher et al 2015[17]	Alberta, Canada 2005–2011	14,939: B alone 805, B 5722, M 8412 (?)	T1-4N0-3M0	T-stage, N-stage, ER, PR	CT (adjuvant, neoadjuvant), ET; (RT)	No	50 mo	5-yr OS: B alone 74% B 94% M 83%	Stage (I, II, III), Mx-RT, Mx+RT
Hofvind et al 2015[39]	Norway 2005–2011	9547: B 5906, M 3641	T1-4N0-3M0	T-stage, N-stage, molecular subtypes, grade	CT, ET, RT	No	?	6-yr OS: B 97.1% M 89.3%	No
Chen, Liu et al 2015[43]	NCDB, USA 2004–2011	160,880: B 126,569, M 34,311 (8181)	T1-2N0-3M0	T-stage, N-stage, ER, PR, grade, localization, LVI	CT	Yes	43.4 mo	5-yr OS: B 93.2% M 83.5%	N-stage (N0, N1, N2), Age (<50; ≥) and N-stage, CCI and N-stage, Mx-RT, Mx+RT
Ye et al 2015[32]	SEER, USA 1998–2003	6671: B 3249, M 3422 (795)	T1-3N0-1M0 Age < 40	Stage, T-stage (T1-T3), LN (N0, N1), ER	CT, ET	No	111 MO	10-yr OS: B 82% M 65%	Age, stage, Mx-RT, Mx+RT
van Maaren et al 2016[13]	Netherlands 2000–2004	37,207: B 21,734, M 15,473	T1-2N0-1M0	Size, LN, ER, PR, grade, localization	CT, ET	No		10-yr OS: B 82% M 65%	T1N0, T1N1, T2N0, T2, N1
van Maaren et al 2016[41]	Netherlands 2000–2004	3071: B 1055, M 2016 (2016)	T1-2N2M0	Size, LN, type, grade, ER	CT, ET	No	126 MO	10-yr OS: B 63% M 52%	T1N2, T2N2
Bleicher et al 2016[34]	SEER, USA 1992–2009	5685: B 887, M 4798	T3N0-3M0 Age 65	Stage II-III, LN, type, grade, size, ER	CT, RT; NACT	Yes		5-yr OS: B 51.8 M 49.6	
Chen, Wang et al 2017[33]	SEER, USA 2010–2013	11,514: B 5469, M 6045	T1-4N0-3M0 TNBC	Grade, stage, TNM	RT	No	22 mo	4-yr OS: B 91% M 82%	Grade, stage, T-stage, N-stage, age
Hartmann-Johnsen et al 2017[40]	Norway 1998–2009	6387: B 4449, M 1938	T1-2N0-1M0	Size, LN, type, grade, ER-stratification in TNM	No	No	72 mo	10-yr OS: B 96% M 92%	T1N0, T2N0, T1N1, T2N1
Lagendijk et al* 2017(1)[9]	Netherlands 1998–2005	60,381: B 31,413, M 4950	T1-2N0-2M0	Tumor localization, T-stage, N-stage, type, grade	CT, ET, RT	Yes	144 mo	T1-2N0-1 10-yr OS: B 89% M 78%	T1-2N0-1, T1-2N2, T1-2N0-1; age; ER/PgR; adjuvant therapy; comorbidity
Lagendijk et al* 2017(2)[9]	Netherlands 2006–2012	69,311: B 41,580, M 27,731	T1, 2N0-2M0	Tumor localization, T-stage, N-stage, type, grade. HR, HER2, focality	CT, ET, RT	Yes	84 mo	T1-2N0-1 10-yr OS: B 94% M 87%	T1-2N0-1, T1-2N2, T1-2N0-1; age; ER/PgR; adjuvant therapy; comorbidity

Mogal et al 2017[36]	SEER, USA 1998–2009	1784: B alone 270, B 918, M 596	T1-2N01M0 Age 70+	Size, LN	RT	Yes		BCS+RT 10-yr OS: B alone 63% B 73% M 63%	
Grover et al 2017[37]	SEER, USA 1995–2009	150,171: B 94,477 M 51,219	T1-2 (≤30 mm), N0M0 Age ≥50	Size (5 mm groups), ER, PgR	RT	No	61/63	10-yr OS B 79.5 B (APBI) 78.8 M 67.4	
Christiansen et al 2018[10]	DBCG, Denmark 1995–2012	58,331: B 26,958, M 27,143 (6556)	T1-3N1-3M0	Size, LN, type, grade, ER, HER2, LVI, focality	CT, ET, RT	Yes	138 mo	10-yr OS: B 82% M 57%	N-stage (N0, N1, N2, N2; age, year of incl. CCI, adjuvant treatment, Mx-RT, Mx+RT
Lazow et al 2019[44]	NCDB, USA 2004–2014	11,859: B 5074, M 6785	T1N0M0 Age <40	Grade, "subtypes" based on HR and HER2	CT, ET, anti-HER2, RT, bilat mastectomy, reconstruction	Yes	62 mo		
Mazor et al 2019[11]	NCDB, USA 2004–2011	30,324: B 3296, M 27,028	T3N0-3M0	Size, LN, grade, type	CT, RT	Yes	?	5-yr OS: B 68% M 69%	
Landercasper et al 2019[12]	NCDB, USA 2004–2013	845,136: B 464,053, M 381,084	T0-4N0-3M0	T-stage, N-stage, grade, type, ER	CT, RT	Yes	?	5-yr OS: B 88.6% M 83%	Stage (I, II, III); HR (positive, negative)
Li et al 2019[35]	SEER, USA 2010–2014	14,910: B 7381, M 7529 (562)	T1-2N0M0 TNBC	Size, grade, stage, type (HR, HER2)	CT, (RT)	No	?	5-yr OS: B 88.6% M 83%	Age; size; grade; stage, Mx-RT, Mx+RT
Almahariq et al 2020[45]	NCDB, USA 2006–2014	231,642: B 144,263, M 87,379	T1-2N0M0	T-stage, ER, PgR, HER2, grade, LVI, no LN evaluated, localization, RS	CT, ET	Yes	B 49 M 47	5-yr OS: B 94.4% M 91.8%	Age, RS
Wrubel et al 2020[46]	NCDB, USA 2004-2014	202,376: B 101,188, M 101,188	T1-2N0-1M0	Size, No pos. nodes, type, grade, ER, PgR, HER2, LVI	CT, ET	No	B 43 M 41	5-yr OS: B 92.9% M 89.7%	
de Boniface et al 2021[14]	NKBD, Sweden 2008–2017	48,986: B 29,367, M 19,616 (7206)	T1-2N0-2M0	T-stage (T1mi, T1a etc.), N-stage, ER, PR, HER2, type, grade,	RT, CT, ET, HER2, (NACT)	Yes	75	5-yr OS B 95.1% M 84.5% M+R 86.0	T1N0, T1N1, T1N2, T2N0, T2N1, T2N2, Mx-RT, Mx+RT
Guo et al 2021[38]	SEER, USA 2010–2015	13,986: B 6116, M 7146 (2663)	T1-4N0-3M0 TNBC	T-stage, N-stage, grade, laterality, tumor site (HR, HER2)	RT	No	?	5-yr OS B 87.9% M 79.6% M+R 65.5%	Age, T-stage, N-stage, Mx-RT, Mx+RT
Zhang et al 2021[47]	SEER, USA 2001–2016	2412: B 881 M 1531	T1-3N0-3M0 Metaplastic BC	T-stage, N-stage, HR, grade	RT, CT	No	73	5-yr OS 84.3 ***vs*** 62.5	
Chu et al 2021[48]	Lousianna, USA 2004–2016	18,260: B 9968, M 8292	T1-2N0-1M0 T3N0M0	T-stage, N-stage, grade, type, ER, focality	(RT), CT, ET	Yes	81	5-yr OS B 92.0% M 84.8%	
Abrahimi et al 2021[49]	New Zealand 2000–2015	6384: B 4608, M 1776 (269)	T1-2 (size < 30 mm) N1-2M0	T-stage (T1. T2), N-stage, ER, PgR, type, grade, LVI	RT, CT, ET	No	106		Mx-RT, Mx+RT
Kim et al 2021[50]	South Korea 1998–2012	45,770: B 28,623, M 17,147	T1-2N0-1M0	T-stage, N-stage, grade, LVI, subtype (ER HER2)	No	No	68	10-yr OS B 93.2% 87.9%	

*Lagendijk et al includes 2 distinct periods and is therefore included as 2 separate studies. Numbers in parentheses represent subgroups of patients having mastectomy plus radiation therapy included in separate comparison with BCS plus radiation therapy.
B, breast-conserving surgery + RT; BCSS, breast cancer-specific survival; CT, chemotherapy; DBCG, Database of Danish Breast Cancer Group; ER, estrogen receptor; ET, endocrine therapy; HR, hormone receptor status; LN, lymph node status; LVI, lymphovascular invasion; M, Mastectomy; M+R, mastectomy + RT; MO, months; NCDB, National Center Data Base; OS, overall survival; PgR, progesteron receptor; RS, recurrence score; RT, radiation therapy; SEER, Database of Surveillance, Epidemiology, and End Results Program; TNBC, triple negative breast cancer; Type, histological type.

When assessing the risk of bias using NOQAS (Figure S1, see http://links.lww.com/AOSO/A171), no studies were considered of high risk of bias. In 9 studies, the risk was found unclear, mainly because the studies lacked treatment data. In 22 studies, the risk of bias was considered low. The full assessment is described in the supplementary materials (Table S1, see http://links.lww.com/AOSO/A171).

The number of prognostic demographic, disease, and treatment-related variables adjusted for in the survival analyses ranged from 4[36] to 12.[9,10] Of the studies included in the overall analyses, all 16 had adjusted for tumor stage, lymph node status, and age, and 14 studies had adjusted for tumor grade. Fewer studies had adjusted for factors such as hormone receptors (K = 11), HER2 status (K = 6), comorbidity (K = 8), CT (K = 10), and ET (K = 7). Older studies had generally adjusted for fewer variables than more recent studies (r = 0.59; $P = 0.016$). An overview of the covariates adjusted for in the analyses is provided in the supplementary materials (Table S2, see http://links.lww.com/AOSO/A171).

Associations between surgery type and overall survival

Thirteen independent studies with a total of 1,311,600 breast cancer patients provided data on OS with a median follow-up of 75 months. The patients who had received BCS had better overall survival than patients who had been treated with mastectomy (Fig. 2A, Table 2), with the difference corresponding to a HR of 1.34. The results of the individual studies varied considerably and were highly heterogeneous, that is, with almost all the variation (98.9%) estimated to be due to systematic differences in effect sizes rather than random error. The considerable variation in effect sizes explains the broad 95% prediction interval, signaling that in 95% of future similar studies, the hazard ratios are expected to fall between 0.84 and 2.15. There was no evidence of publication bias (Egger's test, $P = 0.120$).

The overall findings were supported by the supplementary Bayesian meta-analysis, which provided very strong evidence for a nonzero difference in overall survival between BCS and mastectomy in favor of BCS corresponding to a Bayes Factor (BF)[51] of 179, that is, indicating that the alternative hypothesis is 179 times more likely than the null hypothesis. Likewise, the Bayesian analysis provided extremely strong evidence concerning heterogeneity of the effect sizes with a BF for heterogeneity of 5.72e+210. The combined HR found in the Bayesian meta-analysis was 1.34, which is identical to the effect found with the frequentist approach (1.34). The credible interval, that is, the interval that the true effect sizes are assumed to lie within with 95% probability, was 1.17 to 1.51 and similar to the confidence interval (1.20–1.51).

In subgroup analyses (Table 2), the difference in OS in favor of BCS was larger when compared to mastectomy without RT (HR = 1.46; Fig. 3) than when compared with mastectomy with RT (HR = 1.32). Larger differences were also found for older patient samples (≥50 year; Figure S2, see http://links.lww.com/AOSO/A171), European samples, and samples in high-quality studies. The magnitude of the difference did not appear to be associated with lymph node status (Figure S3, see http://links.lww.com/AOSO/A171). When using meta-regression (Table 3) to explore the moderating influence of lymph node status, age group, region, number of relevant prognostic factors adjusted for in the analysis, time-to follow-up, and study quality, only time-to-follow-up ($P = 0.027$) and study quality ($P < 0.001$) emerged as a statistically significant moderators, with shorter time-to follow-up and high study quality being associated with greater differences in OS in the favor of BCS, and the models explaining 40% and 53% of the variation in hazard ratios, respectively. When examining the role of adjusting for individual prognostic variables, which exhibited sufficient variation (i.e., tumor type, hormone receptor status, HER2 status, ET, and comorbidity), no results reached statistical significance (data not shown). As the samples overlap with the same patients receiving BCS being compared to the 2 groups receiving mastectomy, we were unable to statistically compare BCS versus mastectomy with and without RT.

Associations Between Surgery Type and Breast Cancer-specific Survival

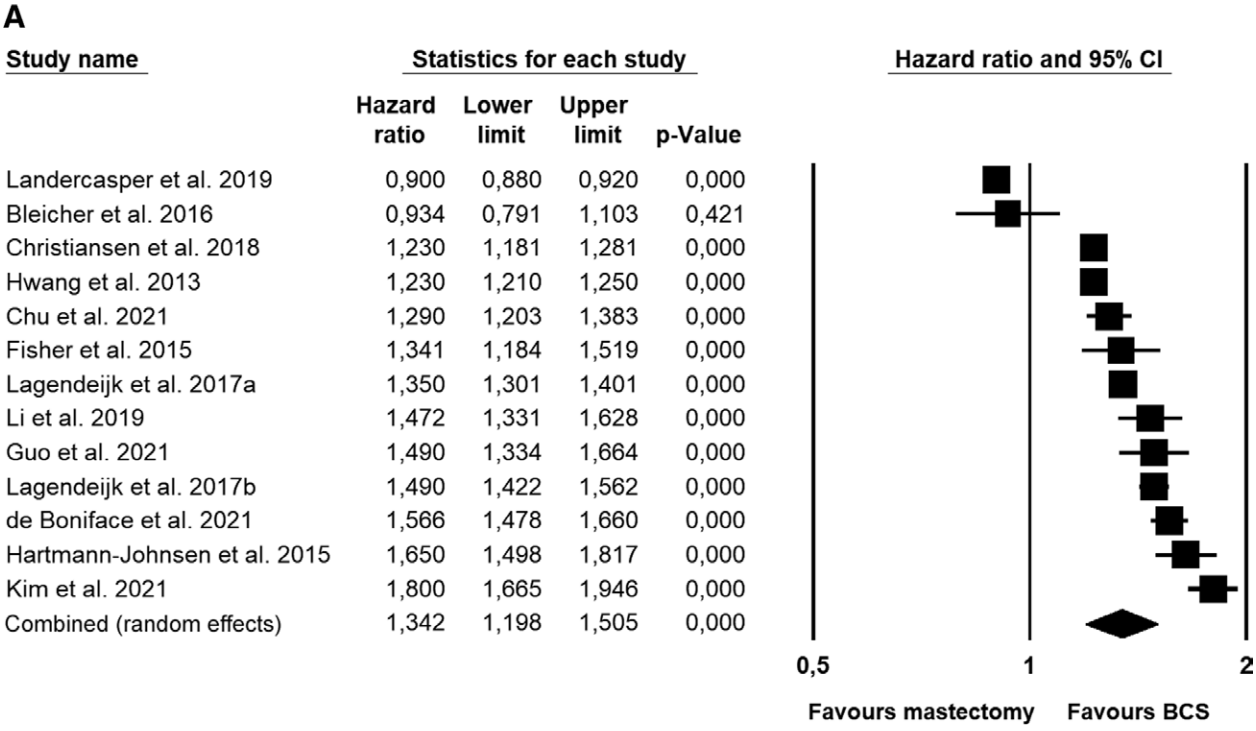
Fourteen independent studies with a total of 494,267 breast cancer patients provided data on BCSS across a median follow-up of 78 months. The patients who had received BCS had better BCSS compared with patients who were treated with mastectomy, with the difference corresponding to a HR of 1.38 (Fig. 2B, Table 2). The results of the individual studies were highly heterogeneous, with 84.0% of the variation estimated to be due to systematic between-study differences. The 95% prediction interval for BCSS was 1.09 to 1.75, and thus narrower than for OS. The results were not suggestive of publication bias (Egger's test: $P = 0.29$).

Bayesian meta-analysis provided extremely strong evidence for a nonzero difference in BCSS between BCS and mastectomy in favor of BCS corresponding to a BF of 4010, that is, indicating the alternative hypothesis to be 4010 times more likely than the null hypothesis. The Bayesian analysis also provided extremely strong evidence concerning heterogeneity of the effect sizes with a BF for heterogeneity of 2.43e+09. The combined HR found in the Bayesian meta-analysis was 1.38, similar to the effect found with the frequentist approach (1.38). The credible interval was 1.25 to 1.51 and only slightly broader than the confidence interval (1.29–1.48).

As seen for OS, the differences in BCSS in favor of BCS were somewhat larger when compared to mastectomy without RT (HR = 1.43) than when compared with mastectomy and RT (HR = 1.36; Fig. 4). Likewise, larger differences were found for older patient samples (≥50 year; Figure S4, see http://links.lww.com/AOSO/A171), European samples, and samples in high-quality studies, whereas the difference did not appear to be associated with lymph node status (Table 2; Figure S5, see http://links.lww.com/AOSO/A171). When exploring the effects of moderators with meta-regression (Table 3), no associations reached statistical significance. This was also the case, when examining the role of adjusting for the individual prognostic covariates, which exhibited sufficient variation (i.e., tumor type, hormone receptor status, HER2 status, ET, and comorbidity—data not shown). Due to partly overlapping samples, we were unable to statistically compare BCS versus mastectomy with and without radiotherapy.

Propensity score matching (PSM) or adjustment

Five studies used propensity score matching. [12,31,34,45,46] Wrubel et al performed PSM in a 1:1 fashion leading to 2 groups of 101.118 subjects each. Five-year OS was significantly better after BCS than after mastectomy (92.9% *vs* 89.7%, $P < 0.001$). Hazard ratios were not calculated. Landercasper et al[12] included a sub-analysis based on PSM 1:1 with 124.139 patients in each group and reported an overall HR = 0.98 (0.96–0.99) in favor of mastectomy. Further stratification by stage gave the following results: stage I HR = 0.78 (0.76–0.81); stage II HR = 1.02 (0.99–1.05), and stage III HR = 1.20 (1.16–1.25), with mastectomy leading to a more favorable outcome in early-stage breast cancer in contrast to in more advanced disease stages. Agarwal et al[31] presented a Cox multivariate analysis on 2 groups of patients with a similar likelihood for a given treatment based on propensity scores. The resulting hazard ratios were in agreement with those from the general multivariate model depicted in Figure 2 (BCS *vs* mastectomy alone: HR = 1.23 [1.25–1.39]; BCS *vs* mastectomy + RT: HR = 1.90 [1.73–2.08]). Almahariq et al[45] and Bleicher et al[34] also used propensity score adjustment in



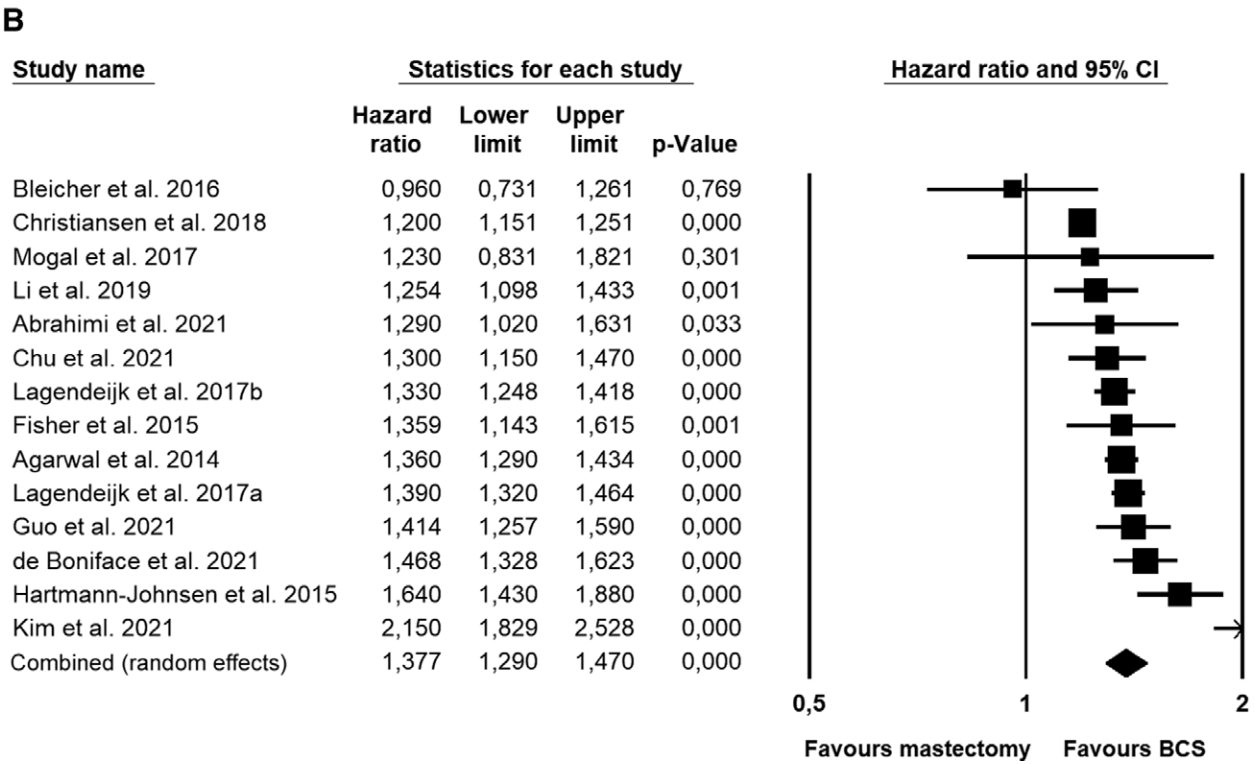


FIGURE 2. Forest plots showing meta-analysis of survival data in population-based independent cohorts of breast cancer patients. (A) Overall survival. The 13 studies included 1,311,600 patients. (B) Breast cancer-specific survival. Fourteen studies with 494,267 patients.

their multivariate model, which are included in the present meta-analyses.

DISCUSSION

The results of the present systematic review and meta-analysis of recently published populations-based observational cohort studies of more than 1.3 million breast cancer patients provide compelling documentation that early breast cancer patients treated with BCS and RT, have, on average, 34% better OS and 38% better BCSS than patients treated with mastectomy. The results of the conventional frequentist meta-analyses were supported by the Bayesian analyses, which indicated strong support for nonzero differences in favor of BCS. The results in favor of BCS hold true regardless of whether mastectomy was combined with RT or not, and for all analyzed subgroups: lymph node

TABLE 2.

OS and BCSS of BCS Compared With Mx—Meta-analyses of Results of Studies Using Data From Population-based Samples

		Heterogeneity				Pooled effect size			
BCS *vs* Mx	**K***	**Q†**	***P***	**I^2‡**	**Tau2§**	**HR‖**	**95% CI**	***P*¶**	**95% PI #**
OS**	13	1045.7	<0.001	98.9	0.042	1.34	1.20–1.51	<0.001	0.84–2.15
OS, Mx– RT ** †† ‡‡	10	137.4	<0.001	93.4	0.011	1.46	1.36–1.57	<0.001	1.13–1.89
OS, Mx+ RT ** †† ‡‡	7	18.2	0.006	67.0	0.007	1.32	1.22–1.42	<0.001	1.04–1.67
OS, N0§§	10	45.6	<0.001	80.3	0.004	1.39	1.33–1.46	<0.001	1.19–1.63
OS, N+‖‖	7	39.5	<0.001	84.8	0.011	1.38	1.26–1.50	<0.001	1.02–1.85
OS, age <50	6	42.1	<0.001	88.1	0.048	1.27	1.05–1.54	0.015	0.65–2.47
OS, age ≥50	5	68.1	<0.001	94.1	0.009	1.40	1.28–1.54	<0.001	1.00–1.97
OS, North America	7	581.6	<0.001	99.0	0.045	1.22	1.04–1.43	0.017	0.68–2.19
OS, Europe	5	73.6	<0.001	94.6	0.011	1.44	1.31–1.59	<0.001	0.99–2.09
OS, TNBC	2	0.0	0.873	00	0.0	1.48	1.37–1.60	<0.001	NA
OS, Low study quality (score 0–6)	3	219.4	<0.001	96.4	0.049	1.04	0.80–1.35	0.773	0.04–27.7
OS, High study quality (score 7–10)	10	229.5	<0.001	96.1	0.014	1.44	1.33–1.55	<0.001	1.08–1.92
Breast cancer–specific survival (BCSS) **	14	81.1	<0.001	84.0	0.011	1.38	1.29–1.47	<0.001	1.09–1.75
BCSS, Mx–RT †† ‡‡	9	54.0	<0.001	85.2	0.027	1.43	1.27–1.62	<0.001	0.94–2.16
BCSS, Mx + RT†† ‡‡	8	26.5	<0.001	73.6	0.014	1.36	1.22–1.51	<0.001	0.99–1.87
BCSS, N0§§	8	15.1	0.034	53.8	0.004	1.30	1.21–1.39	<0.001	1.09–1.55
BCSS, N+‖‖	7	10.1	0.120	40.6	0.002	1.31	1.23–1.39	<0.001	1.13–1.52
BCSS, age <50	5	9.8	0.044	59.1	0.006	1.16	1.05–1.28	0.002	0.75–1.79
BCSS, age ≥50	5	21.1	<0.001	81.0	0.009	1.24	1.11–1.38	<0.001	0.88–1.75
BCSS, North America	7	8.2	0.222	27.1	0.002	1.32	1.24–1.40	<0.001	1.15–1.52
BCSS, Europe	5	37.6	<0.001	89.4	0.009	1.38	1.26–1.51	<0.001	0.99–1.93
OS, Low study quality (score 0–6)	3	4.4	0.018	55.0	0.023	1.19	0.94–1.49	0.145	0.10–13.33
OS, High study quality (score 7–10)	11	75.3	<0.001	86.7	0.011	1.40	1.31–1.50	<0.001	1.09–1.80

*K = number of studies/independent samples in the analysis.

†Q statistic: *P* values <0.1 taken to suggest heterogeneity.

‡I^2 statistic: the proportion of the variance explained by differences in effect sizes beyond random error (heterogeneity).

§Tau2: the between-study variance in effect sizes.

‖Pooled effect size (random-effects model): HR.

¶*P* values (2-tailed): Statistically significant ($P < 0.05$) in bold. HR > 1 indicates an association in the hypothesized direction, that is, BCS is associated with improved survival compared with mastectomy.

#95% PI, that is, the interval in which 95% of future observations from the same family of studies will fall, given the observed data, calculated for heterogeneous ESs ($I^2 > 0$).

**For pooled estimates from K ≥ 10, the possibility of publication bias was explored with funnel plots and Egger's test. No indications of publication bias were found (Egger's test > 0.05).

††Mx ± RT = Mastectomy with and without radiotherapy.

‡‡Number of studies/independent samples for Mx ± RT do not add up with overall OS and BCSS analyses due to omission of overlapping samples to ensure independence.

§§N0 = lymph node-negative breast cancer.

‖‖N+ = lymph node-positive breast cancer.

95% PI, 95% prediction interval; BCS, breast-conserving surgery; HR, hazard ratio; Mx, mastectomy; OS, overall survival.

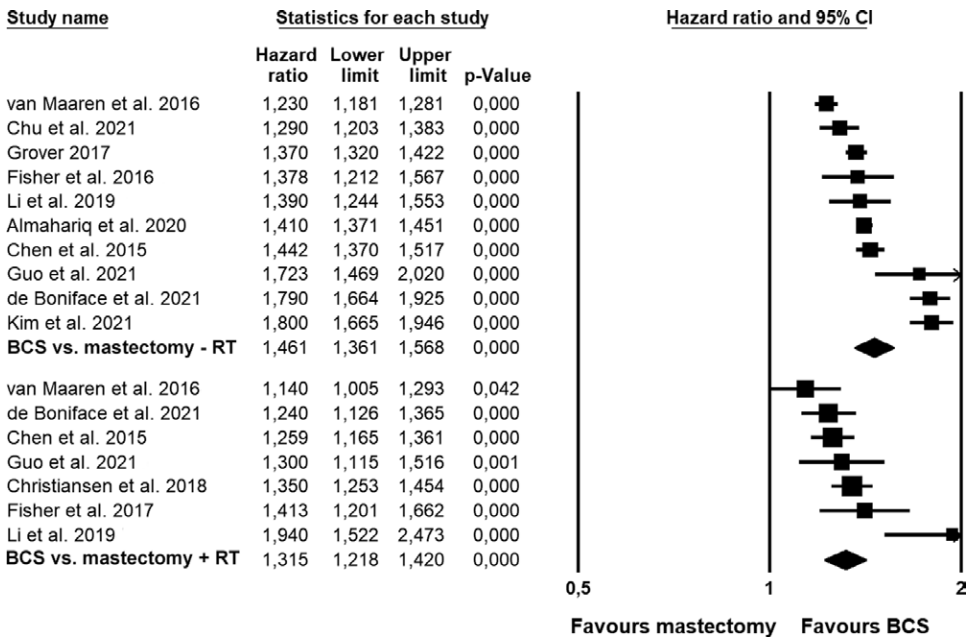


FIGURE 3. Forest plots showing comparisons in overall survival between BCS and mastectomy without (–RT) or with radiation therapy (+RT). BCS indicates breast-conserving surgery; RT, radiation therapy.

TABLE 3.

Results of Meta-regression-based Analyses of Possible Categorical and Continuous Moderators of the Difference in Overall and Breast Cancer-specific Survival Between BCS and Mx

Moderator	Outcome	K	Slope	95% CI	*P*	R^2
N+ (referent: N0)*	OS	17	–0.01	–0.109 to 0.089	0.840	0.01
	BCSS	15	0.013	–0.039 to 0.065	0.623	0.00
Age ≥ 50 (referent: age < 50)	OS	11	0.082	–0.192 to 0.357	0.556	0.07
	BCSS	10	0.056	–0.098 to 0.210	0.478	0.19
Number of covariates adjusted for (range: 5–12)	OS	13	–0.011	–0.054 to 0.032	0.616	0.02
	BCSS	14	–0.023	–0.049 to 0.003	0.080	0.32
North America (referent: Europe)	OS	12	–0.173	–0.351 to 0.005	0.057	0.25
	BCSS	12	–0.046	–0.149 to 0.057	0.379	0.00
Time-to-FU (months) (range: 43–138 months)	OS	9	–0.002	–0.005 to –0.000	**0.027**	0.40
	BCSS	10	–0.002	–0.005 to 0.001	0.186	0.26
High study quality (referent: low)	OS	13	0.332	0.152 to 0.512	**<0.001**	0.53
	BCSS	14	0.166	–0.056 to 0.388	0.142	0.10

* N0/N+ = lymph node-negative and lymph node-positive breast cancer.

Moderators with significant influence on survival are marked with bold *P* values.

BCS indicates breast-conserving surgery; BCSS, breast cancer-specific survival; Mx, mastectomy; Mx ± RT, mastectomy with or without radiotherapy; OS, overall survival.

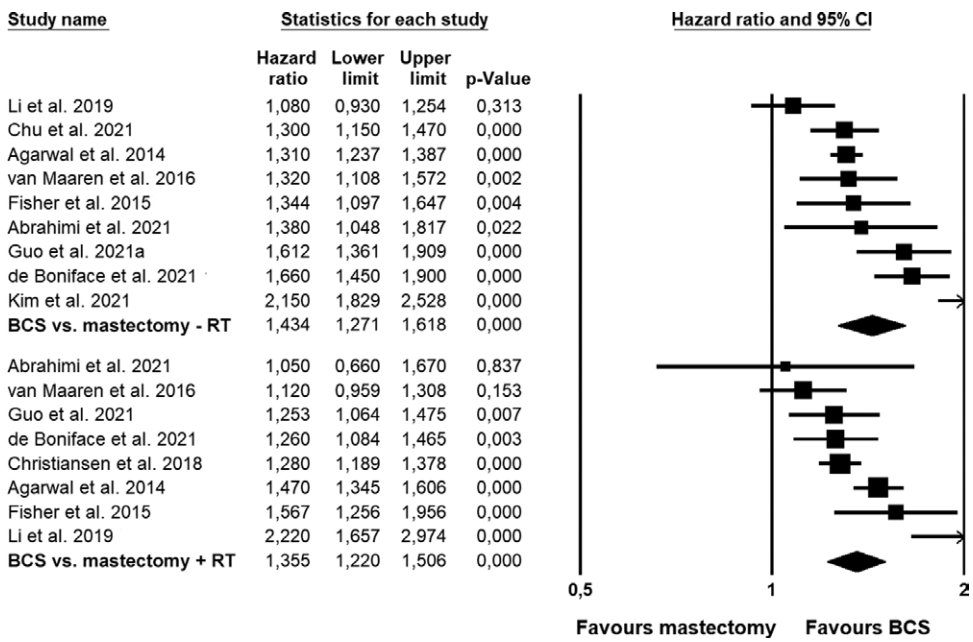


FIGURE 4. Forest plots showing comparisons in breast cancer-specific survival between BCS and mastectomy without (–RT) or with radiation therapy (+RT). BCS indicates breast-conserving surgery; RT, radiation therapy.

negative, lymph node positive, those younger than 50 years, those 50 years or older, TNBC patients, and patients treated in Europe as well as in North America.

There are currently no agreed upon explanations for the observed differences in survival between BCS and mastectomy in breast cancer and for why the recent observational studies report a more favorable outcome after BCS in contrast to the earlier randomized trials.[5] First, it is important to note that in the studies included in the present review, it cannot be ruled out that patients who receive BCS differ from those treated with mastectomy. Due to the nature of the observational data, we do not know the many different reasons for the actual choice made in each of the individual clinical situations. When interpreting the results, it is therefore important to note that all the included studies had adjusted for a number of prognostic and treatment variables. However, the number of covariates varied considerably between studies, ranging from 5 to 12. Almost all studies had adjusted for age, tumor stage, tumor grade, and nodal stage, and several had adjusted for hormone receptor status, comorbidity, RT, and CT. Still, relatively few had adjusted for HER2 status and ET, almost none for lymphovascular invasion and focality, and no studies had adjusted for anti-HER2 treatment. When we used meta-regression to explore whether the difference found between BCS and mastectomy was influenced by the number of prognostic covariates adjusted for in the analyses, this did not appear to be the case for neither OS nor BCSS. When examining the possible role of adjustment for a number of individual prognostic factors, including comorbidity, tumor type, hormone receptor status, HER2-status, ET, none of the associations reached statistical significance. Taken together, the data suggest that the differences observed in survival are not sufficiently explained by differences in prognostic characteristics.

A possible explanation for the difference in outcome between the RCTs and the newer observational studies could be changes in treatment over time which have led to better loco-regional control after BCS and RT. In the early study by Veronesi et al,[2] local recurrence was observed in 8.5% after BCS in contrast to 2.3% after mastectomy, and such results were typical for that period. Since then, the occurrence of local recurrence has been halved,[52] and today, the incidences of local recurrence after BCS is around 2% over 5 years.[53] According to the 2011 EBCTCG meta-analysis,[54] the lower local recurrence rates after BCS

should translate into a better survival. Although the mastectomy group probably also will benefit from fever local recurrences, the absolute numbers are lower, and the impact on survival will be less pronounced. Thus, the development has favored the outcome after BCS in comparison with mastectomy. Second, there have also been speculations that RT makes the difference,[9,55] but this was not supported in a stratified analysis included in the Danish study.[10] In a subgroup analysis of patients with macrometastases, who all had loco-regional RT irrespective of type of surgery, better relative survival (28%) was still found after BCS compared with mastectomy. A third explanation could be that the surgical trauma is more marked after mastectomy resulting in more pronounced immuno-suppression, which, in turn, may promote growth of residual local tumor cells, circulating tumor cells, and micrometastases.[56] Finally, we would also like to draw attention to the so-called abscopal effect,[57] which has been extensively discussed in relation to breast cancer.[58] This proposed mechanism involves RT and the immune system. RT to the residual breast may destroy small foci of cancer cells left behind after the breast-conserving procedure. RT will not only induce immunosuppressive effects but also, during the process of destroying these cancer cells, mobilize host immune effector mechanisms involving pro-immunogenic effects leading to the inactivation and destruction of remaining tumor cells and micrometastases in the body. Such a mechanism could perhaps explain a proportion of the difference in outcome between mastectomy and lumpectomy, even when mastectomy is combined with RT, as remaining tumor foci, apart from within lymph nodes, would be very rare after mastectomy.

The results for TNBC should be interpreted with caution. First, the prevailing data do not include information on BRCA-mutations. Second, in the study which only included patients under 40,[32] where the proportion of BRCA1-positive is expected to be significant, the benefit seems smaller. Third, the finding of a less favorable outcome after mastectomy and RT in one study[38] indicates that the groups in the comparison are not congruent, even in the adjusted comparison. On the other hand, a previous meta-analysis from 2015 by Vila et al,[59] restricted to patients younger than 40 years, came to the conclusion that BCS was at least as safe as mastectomy (HR = 0.90 [0.81–1.00]). Very recently, a meta-analysis confined to BRCA1 and BRCA2,[60] concluded that survival outcomes following BCS is comparable to mastectomy in BRCA carriers. However, only few studies with a small number of patients were included in the meta-analysis, and as the study also reports a more than 400% increase in local recurrence after BCS, the results are difficult to interpret. Taken together, more studies including information on BRCA-status are needed before conclusions can be drawn regarding the safety of BCS in TNBC and in the very young patients.

Breast-conserving therapy is not always applicable,[61] and it is argued that breast cancer in the very young women (<35 years) may have a survival benefit after mastectomy,[61] and that could be related to a higher risk of loco-regional recurrence after BCS in this age-group.[53] The recommendations to these patients are therefore more complicated. Breast cancer in combination with extensive ductal carcinoma in situ (DCIS), particularly in women under 40 yrs., may also require mastectomy.[61] BCS is also not an option if RT cannot be offered. The present meta-analysis and the currently available literature do not indicate that BCS should be omitted because of nodal status N0-1, but when it comes to more advanced nodal stages, it is more difficult to come to a uniform conclusion.[10,43] For T3 tumors, the sparse data indicate that there could be a small benefit in survival of mastectomy compared to BCS.[11,34] On the other hand, if clear margins and an acceptable cosmetic result can be achieved, multifocal and multicentric breast cancer as well as central location of the cancer in the breast should not be considered as an indication for mastectomy instead of BCS.[61]

All but one of the reviewed population-based cohort studies point in the same direction. In contrast, Landercasper et al[12] found results that stand out in several ways. First, in contrast to all remaining studies, this study showed a more favorable outcome after mastectomy. Second, it was found in the propensity matched cohorts that the benefit of mastectomy was most pronounced among patients with an early tumor stage. Third, a considerable difference was observed between the unadjusted and the adjusted hazard ratios which changed from 0.6 to 1.1. Fourth, there is a pronounced difference in the size of the population between this study and other comparable studies from NCDB. Chen et al[43] report on a cohort from 2004 to 2011 that included only T1-2N0-1 patients, which must be the bulk of patients with breast cancer from that period. Mazor et al[11] report on the population of patients with T3N0-3 from the same period (2004–2011), and together these 2 studies thus report on a total population of 180,309 T1-3N0-3M0 patients. Although they included a two year longer observational period, it is unclear how Landercasper et al could include a population from NCDB that is more than four times larger (N = 845,136). Furthermore, the proportion of patients treated with BCS differs considerably between these studies. Landercasper et al report 54.9% receiving BCS, whereas Chen et al and Mazor et al together report 71.8% patients treated with BCS. There is also considerable overlap between the studies of Landercasper et al[12] and the studies by Almahariq et al,[45] and Wrubel et al,[46] who report on NCDB populations treated between 2006 and 2014 and between 2006 and 2015, respectively. Both studies were restricted to T1-2M0. One was further restricted to N0,[45] and the other[46] included N0-1. The populations contained 231,642 and 431,899 patients, respectively, and among those 62.3% and 70.0% were treated by BCS. Compared with these studies, the Landercasper study includes a population almost twice the size the number reported by Wrubel et al. Neither Landercasper et al[12] nor the two most recently published papers[45,46] provide any information on the considerable differences in population sizes and proportions of BCS between the NCDB studies.[11,43] Although the results reported by Landercasper et al are based on by far the largest cohort, the discrepancies in study population sizes need to be clarified, and the results confirmed.

Strengths and limitations

Our systematic review and meta-analysis has several strengths. First, the numbers of patients in the population-based independent cohorts included in the meta-analyses are very large, and all studies, but one, show the same tendency in favor of BCS for both overall and breast cancer-specific survival. Second, the meta-analyses are based on studies which all have adjusted for a number of relevant prognostic factors. Third, no study was considered being at high risk of bias and we found no clear indication of publication bias. Fourth, we were able to perform a number of stratified analyses showing comparable results across comparisons between BCS and mastectomy with and without post-mastectomy radiation therapy, as well as across different subgroups of patients, including node negative and node positive, young and older age groups. Finally, the results were supported by results of supplementary Bayesian meta-analyses indicating very strong support for nonzero differences in survival.

Although the differences are thus robust, a number of possible limitations should also be noted. First, the included studies are not randomized controlled trials. The validity of the comparisons is therefore dependent on proper adjustment for patient, tumor, and treatment variables, and these variables are limited or missing in several of the studies. Second, the included studies could also suffer from confounding by indication. Comorbidity is strongly associated with poorer survival,[62] and it has previously been shown that patients with more comorbidity

were more likely to be treated with mastectomy.[10] The risk of selection bias was demonstrated in the Danish study,[10] where patients who were initially assigned to BCS, but ended up being treated with mastectomy, had significantly better survival than patients for whom mastectomy was decided up front. This could artificially reduce survival after mastectomy in studies which have not adjusted for comorbidity. Even with these limitations, the results are robust, when it comes to patients with the most frequent stages at presentation (T1-2N0-1M0). The only clear outlier is the study by Landercasper et al,[12] where discrepancies in study population sizes and proportions of patients receiving BCS are found, when compared to other studies from NCDB, and this raise some concerns. Even so, it does not alter the overall result of the meta-analysis.

Conclusions

The combined findings from large population-based studies indicate that BCS is associated with survival benefit compared with mastectomy, suggesting that BCS be the recommended treatment of early breast cancer (T1-2N0-1M0) if a radical lumpectomy can be performed.

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